

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON**

**IN RE: ETHICON, INC., PELVIC REPAIR
SYSTEM PRODUCTS LIABILITY
LITIGATION**

**THIS DOCUMENT RELATES TO
WAVE 1 CASES**

Master File No. 2:12-MD-02327

**JOSEPH R. GOODWIN
U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF BRUCE A. ROSENZWEIG, M.D.

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I. Background and Qualifications

I am currently an Assistant Professor of Obstetrics and Gynecology at Rush University Medical Center in Chicago, Illinois. I received my MD degree in 1984 from the University of Michigan in Ann Arbor, Michigan. Following graduation from medical school, I completed an Obstetrics and Gynecology Residency at Michael Reese Hospital in Chicago. In 1988, I attended a one year pelvic surgery fellowship at State University of New York in Syracuse, New York. Following that fellowship, I attended a two year Urogynecology and Urodynamics fellowship at UCLA Harbor General Hospital in Torrance, California. After graduating from the Urogynecology fellowship, I became a faculty member at the University of Illinois in Chicago. I started a Urogynecology program at the University of Illinois and also was the residency program director. In 1998, I went into private practice, and subsequently established a private practice at Rush University Medical Center. I have also worked at John H. Stroger Hospital here in Chicago from May 2003 until November 2010 and Weiss Memorial Hospital as Associate Chair of Gynecology from February 2011 until July 2012. I have published numerous articles and given numerous lectures on the topics of pelvic organ prolapse, urinary incontinence and repair of pelvic organ prolapse.

Throughout my career, I have performed over a thousand pelvic floor surgical procedures, including abdominal sacrocolpopexy, uterosacral suspensions, sacrospinous ligament fixations, native tissue repairs, biological graft repairs and synthetic mesh repairs. I have also used numerous synthetic pelvic mesh products, including Ethicon's TVT, TVT-Obturator, and Prolift. In addition, I have performed over 300 surgeries dealing with complications related to synthetic mesh, including the removal of numerous TVT devices. I have also treated approximately 800 additional patients with mesh non-surgically. I was invited by Ethicon and

attended both its Gynecare Prolift Training Seminar and TVT Obturator Seminar in Belgium. In addition, I was invited and attended a Bard Avaulta training seminar in the past.

A copy of my CV and Fee Schedule is attached as Exhibit “A” and a copy of my testimony for the last four years is attached as Exhibit “B”. The documents I relied on for this report are contained in Exhibit “C” as well as those documents cited throughout this Report.

II. Summary of Opinions

In formulating my opinions and preparing this report, I reviewed scientific literature, corporate documents from Ethicon and depositions of Ethicon employees and witnesses. The corporate documents and depositions were supplied to me by counsel. A list of Ethicon corporate documents and depositions reviewed for this report is attached as Exhibit “C”; other materials reviewed are listed within the body of the Report. All opinions I have are to a reasonable degree of medical and scientific certainty. I understand discovery is still ongoing in this case, and I reserve my right to amend my opinions if further information is provided in any form including, but not limited to corporate documents, depositions and the expert reports of both Plaintiff and Defense experts.

- A. The Polypropylene Mesh in the PROSIMA Is Not Suitable As a Permanent Prosthetic Implant for Pelvic Floor Repair
 - 1. Polypropylene Mesh Such as GYNEMESH PS Degrades.
 - 2. Polypropylene Mesh Causes Chronic Foreign Body Response.
 - 3. Polypropylene Mesh Such as GYNEMESH PS Causes and Perpetuates Infections.
 - 4. GYNEMESH PS Is a Small-Pore, Heavyweight Mesh that Promotes Fibrotic Bridging and Scar-Plate Formation.
 - 5. Polypropylene Meshes, Including PROSIMA’S GYNEMESH PS, Contract and Shrink.
 - 6. The Mesh Used in the PROSIMA Deforms.

7. The resin used to manufacture the polypropylene mesh in Prosima should never have been used in a permanent mesh implant in the vagina.
- B. Clinical Data on the PROSIMA Device/Procedure Does Not Support Its Efficacy or Its Safety
- C. The PROSIMA IFU Did Not Contain or Understated the Known Risks of the PROSIMA Device

III. Clinical Data on the Prosima Device/Procedure Does Not Support Its Efficacy or Its Safety

A. Early Data for Prototype

In 2004, Ethicon was investigating a “Strategic Opportunity” for a new method for POP repair invented by an Australian physician, Dr. Marcus Carey.¹ Carey had patented a method and device that was unique in primarily two ways: (1) the mesh implant was “anchorless”; and, (2) it called for inserting a “splint” into the vagina that stayed in place for 2-4 weeks post-surgery to allow for tissue ingrowth.² According to Carey, his concept was supposed to be easier to use than existing POP repair devices and produce better results.

Carey had not published any data on his design. By April 2004, he remained the only physician who had used the method having performed “27+ interventions” with reportedly one failure at two months and two mesh exposures (7%).³ Most of the procedures were done using Ethicon’s VYPRO II mesh, not the GYNEMESH PS that ultimately would be included in the PROSIMA.

The data was described as an “uncontrolled case series” without proper documentation of the selection of procedure for each of the cases.⁴ Ethicon’s team wrote: “[c]linical information [was] insufficient for a definitive answer on procedure effectiveness, or to consider

¹ ETH.MESH.00264435.

² WO 2004045457 A1, “Method of Surgical Repair of Vagina Damaged By Pelvic Organ Prolapse And Prosthetic Materials And Devices Suitable For Use Therein”.

³ ETH.MESH.00264435 at 457.

⁴ *Id.* at 474.

commercialization.”⁵ Their recommendation was to pursue Carey’s device, internally named “Project Mint”, as the “Next Generation” pelvic floor repair solution with a targeted launch of January 2006 “with 6 months data.”⁶ The PROSIMA was designed for “Simple POP” procedures that would produce better outcomes than native tissue repairs.⁷ It was targeted at “Generalists.” The “Market Assessment” was described as a \$300+MM Opportunity ... as big as “TVT”.”⁸

On September 30, 2004, Ethicon purchased the rights to Carey’s patented method.⁹ Ethicon agreed to pay Carey \$350,000 within 30 days of execution of the agreement,, \$150,000 on or before January 31, 2005, \$100,000 within 30 days of publication of a clinical study in an internationally recognized peer reviewed journal, \$400,000 within 30 days of marketing and a royalty on net sales of 2.5%.¹⁰

B. Investigator Study: Carey M, et al., Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008; 115:391–397

In 2004, Carey initiated a prospective observational study using a “Mint like” procedure.¹¹ There were significant differences in the device and surgical methods from what would ultimately become the PROSIMA.¹² In 2008, the study was eventually published in the

⁵ *Id.* at 457.

⁶ ETH.MESH.00264435.at 438.

⁷ ETH.MESH.00190766 (June 2005 Project Mint Charter Presentation) stating:

Develop a procedural kit for the surgeon performing pelvic floor repairs entailing a less technically challenging, standardized technique which will improve functional outcomes over traditional native tissue and current flat mesh repairs and will be applicable for most cases of pelvic organ prolapse.

Id., at 772 and 787.

⁸ *Id.*

⁹ I review this information here because, as discussed below, it is well-recognized that the disclosure of financial conflicts of interest are relevant to assessing the validity of study data. *See, e.g.*, Wall LL, Brown D., *The perils of commercially driven surgical innovation*. Am J Obstet Gynecol 2010;202:30.e1-4.

¹⁰ ETH.MESH.00916799 at 17.

¹¹ ETH.MESH.00916799 at 12 (June 13, 2005).

¹² *Id.* (“No DIM, Templates or Guide used, No balloon available, gauze packing used instead”); ETH.MESH.02092920 (study used different insertion tools, different “splints” and gauze packing instead of a balloon); ETH.MESH.01411037.

British Journal of Obstetrics and Gynecology (“BJOG”).¹³ Interestingly, as part of the rationale for the new device/procedure, the investigators noted: “Significant problems associated with the use of mesh during vaginal surgery for pelvic organ prolapse have been reported and include dyspareunia and mesh exposure.”¹⁴ The paper cited in support of this statement was a study of women who had POP repair using Ethicon’s PROLENE mesh.¹⁵ The investigators in that study concluded that, due to mesh-related adverse events, the use of mesh in POP repair should be abandoned. They stated:

In summary this study confirms that, despite good anatomical results, the use of prolene mesh for prolapse repair carries morbidity especially in terms of erosion through the vaginal wall and de novo dyspareunia. On the basis of these data, we believe that the use of prolene mesh for prolapse repair should be abandoned.

Carey and Slack described their study as a “simple and novel approach using mesh and placement of a vaginal support device (VSD) into the lumen of the vagina at the completion of surgery.”¹⁶

Ninety-five women underwent surgery for pelvic organ prolapse using GYNEMESH PS and a vaginal support device. The mean age of the women was 59 years and mean parity of 2.6. Forty women (43%) had undergone a prior hysterectomy and 23 (24%) had at least one surgical procedure for pelvic organ prolapse. A total of 31 (33%) women had undergone prior surgery for pelvic organ prolapse and/or stress urinary incontinence.

At 6 months, 78 (82.1%) women returned for physical examination and 80 (84.2%) at 12 months. Assuming the 15 women not examined at 12 months were objective failures, then the

¹³ Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397; Higgs P, Carey M, Cornish, A, Slack M, Surgery for pelvic organ prolapse using mesh and a new vaginal device: A 6 month follow up, Int.Urog.J. 2006 Supp. 2:S138-S139 (presenting 6-month results for 69 women).

¹⁴ *Id.* at 391.

¹⁵ Milani R, et al., Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. BJOG 2005;112:107–11.

¹⁶ Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397.

failure rate would be 28.4%. They reported four mesh exposures (reported as 4.2% using as the denominator, the total 95 women enrolled). Two of the erosions required excision. The investigators concluded: “Further clinical studies, including comparative studies, are required to establish the role of this surgery.”¹⁷

In addition, the publication does not disclose that, during the study period, the lead investigator: (1) entered into an agreement to sell the procedure/device to Ethicon for \$1 million; (2) already had been paid a significant portion of the \$1 million; (3) was required to publish the data and was paid \$100,000 for doing so; and, (4) would be paid significant royalties upon marketing of the device/procedure. As a physician, we expect and rely upon full disclosure of such financial conflicts of interest to allow us to properly assess the biases that might be present in a study.

Based on my background and professional experience, I agree that this study did not provide sufficient clinical data to support marketing the device and procedure used. It certainly did not provide sufficient data on what would ultimately be marketed as the PROSIMA device because, as noted above, the materials and methods were markedly different than the PROSIMA.

Over a year before the publication of the Carey study, Ethicon personnel had reviewed the data and determined it was insufficient to support the marketing of the PROSIMA. On December 7, 2006, at a meeting of Ethicon’s European team, Axel Arnaud “informed the team about the disappointing results of the Carey/Slack observational study, which was considered as very important for the future launch.”¹⁸ The team also discussed the “[m]itigated interest from European KOLs who were recently invited to participate to an expert meeting in London” and “[i]n light of physicians previous experience, general feeling that this procedure would not

¹⁷ *Id.* at 397.

¹⁸ ETH.MESH.03912703

provide enough support even with the vaginal support device.”¹⁹ Two weeks earlier, Ethicon had submitted the 510(k) for market clearance of the PROSIMA. Ethicon did not provide the clinical data. Instead, Ethicon provided a one-page abstract of data from Carey without disclosing that Ethicon had already paid Carey hundreds of thousands of dollars for the device/procedure and, ultimately, he stood to gain millions of dollars more.

C. Ethicon-Sponsored Study: Zyczynski H, et al., Prosima Study Investigators, One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device, AJOG December (2010)

In response to the Carey data, Ethicon initiated an Ethicon-sponsored study and delayed the target launch date of PROSIMA.²⁰ The 6 month data from this latest study was to determine whether the PROSIMA was a “go or no go.”²¹

The Ethicon-sponsored study was a prospective multi-center cohort study of the anatomic and functional outcomes of prolapse surgery using the PROSIMA as it was later marketed. The study was conducted in 11 sites in United States, United Kingdom, Germany and Australia. 136 women with symptomatic POP-Q stage II or III prolapse planning vaginal surgical repair in one or both compartments were enrolled from May 2007 to September 2007. Success was defined as POPQ stage 0 or I at one year in the treated compartment with the upper 97.6% one-tailed CI not to exceed 20%..²²

¹⁹ *Id.* at 704.

²⁰ ETH.MESH.00455676 (January 24, 2007 e-mail from London Brown) (“As you may recall, our original launch plan called for a mid-2007 launch dependent on the data from the Carey/Slack study. “[The study] did not meet the full requirements for our launch needs, especially considering the substantial differences between the original study's product/procedure, and the final commercial PROSIMA™ product.... This then means that the current PROSIMA™ launch will be postponed until early 2008, and this team will be on hold until the end of the year.”).

²¹ ETH.MESH.03915846.

²² ETH.MESH.01193011. The initial protocol called for success as POPQ stage 0 to I at 1 year in all compartments. This was amended to limit to the treated compartment only.

When Ethicon received the 6 month data, it was clear that the study had already failed its primary endpoint.²³ In addition, the data reflected significant variability between study centers.²⁴ On April 11, 2008, before receipt of the 12 month data, Ethicon delayed the launch of PROSIMA again.

[T]he preliminary data also shows a wider than anticipated variance in the objective success rates across the 11 investigation centres. As part of our commitment to ensure the PROSIMA™ enters the market well supported with clinical data and well trained customers, the decision has been made to postpone the PROSIMA premarket preparation activities to undertake further analysis of the clinical results. This course of action is made in concert with clinical development, medical affairs, Ethicon Women's Health and Urology senior management who have all reviewed the situation.... This action is prudent to ensure that the factors contributing to outcome variance are identified and well understood with measures taken to incorporate the best surgical technique in the IFU and training protocols.²⁵

As noted above, if this data was not promising, PROSIMA was supposed to be a “no go.”²⁶ Ethicon kept going.

In April 2009, the 12 month results were presented at the Annual Meeting of the American Urological Association in Chicago, and, in 2010, published in the American Journal of Obstetrics and Gynecology.²⁷ It was reported that 130 of the 136 women who received surgery returned for the 1-year assessment. Of these, 76.9% (95.2% CI 68.7%-83.9%) were stage 0 or I. The study had indeed failed its primary endpoint. In 86.9% of the cases, the leading vaginal edge was above the hymen. Pelvic symptoms, quality of life, and sexual function improved

²³ ETH.MESH.03162936 (“We did state in the protocol that the study would be considered a success if the failure rate had an upper 95% CI of less than 20% at 12 months. We have already failed that. I am concerned here that this looks like a good bit of spin going on, and due to his commercial interest, this is not going to come over as objective as perhaps it should.”).

²⁴ ETH.MESH.01193011 at 032 (“Whilst this success rate was lower than expected, there was substantial inter-site variability in anatomic success observed in this study which ranged from 16.7% to 100%.”).

²⁵ ETH.MESH.04569706.

²⁶ ETH.MESH.03915846.

²⁷ Halina M. Zyczynski, MD, Marcus P. Carey, MD, Anthony R.B. Smith, MD, Judi M. Gauld, BSc (Hons), David Robinson, MD, Vanja Sikirica, PharmD, MPH, Christl Reisenauer, MD, Mark Slack, MD, Prosima Study Investigators, One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device, *AJOG* December (2010), December 2010 Volume 203, Issue 6, Pages 587.e1–587.e8: Published Online: October 11, 2010.

significantly from baseline ($P < .05$). The investigators concluded that: Vaginal support, pelvic symptoms, and sexual function improved at 1 year, compared with baseline, after trocar-free prolapse repair with nonanchored mesh and a vaginal support device. This conclusion is misleading at best.

Based on my professional experience and review of the documents and studies related to PROSIMA, it is my opinion that, at this point, Ethicon had no clinical evidence supporting the safe and effective use of the PROSIMA device. The early prototype studies did not use the marketed device and were effectively uncontrolled case series about a different device and method. This Ethicon-sponsored study was the best evidence generated on the PROSIMA. As shown above, prior to the initial marketing of the PROSIMA (December 2009), Ethicon had the 6 and 12 month data from this study that demonstrated: (1) failure of the primary success endpoint; and, (2) mesh-related adverse events, such as 8% erosions.²⁸ In December 2009, Ethicon launched the PROSIMA. The only other clinical data Ethicon had in its possession was Carey's comparative study which, as discussed below, demonstrated that PROSIMA was not superior to traditional surgeries and had increased risks and complications.

D. Carey M. Higgs P. Goh J, Lim J, Leong A. Krause H. Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG. 2009 Sep;116(10):1380-6

In July 2009, Dr. Carey published his non-inferiority RCT: *Vaginal Repair With Mesh Versus Colporrhaphy for Prolapse: A Randomized Controlled Trial*, in the British Journal of Obstetrics and Gynecology. This was a prospective randomized controlled trial comparing

²⁸ In a follow up study of this population at 24 months, the success rate declined: ICS POP-Q stage 0-I, at >2 years was 69.1% (95% CI, 59.6-77.6%). There was an additional erosion that was first identified at 28 months (demonstrating that mesh erosions can occur years after the mesh is implanted). Sayer T., Lim J, Gauld J, Hinoul P., Jones P., Franco N, Van Orie D., Slack M; Prosima Study Investigators. Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. *Int Urogynecol J.* 2012 Apr;23(4):487-93 (published online December 6, 2011).

PROSIMA to traditional colporrhaphy for the treatment of pelvic organ prolapse.²⁹ The study reported on 139 women with POP-Q greater than or equal to grade 2 prolapse requiring both anterior and posterior compartment repair. Subjects were randomized to anterior and posterior vaginal repair with mesh augmentation. The primary outcome was the absence of POP-Q stage greater than or equal to 2 at 12 months. Secondary outcomes were symptoms, quality-of-life outcomes and satisfaction with surgery and complications were also reported.

For subjects attending the 12-month review, success in the mesh group was 81.0% (51 of 63 subjects) compared with 65.6% (40/61) in the no mesh group and was not significantly different ($P = 0.07$). A high level of satisfaction with surgery and improvements in symptoms and quality-of-life data were observed at 12 months compared to baseline in both groups, but there was no significant difference in these outcomes between the two groups. Vaginal mesh exposure occurred in four women in the mesh group (5.6%). De novo dyspareunia was reported by five of 30 (16.7%) sexually active women in the mesh group and five of 33 (15.2%) in the no mesh group at 12 months. The study concluded: “vaginal surgery augmented by mesh did not result in significantly less recurrent prolapse than traditional colporrhaphy 12 months following surgery.” That is, Carey failed to show superiority whether measured by POP-Q or QOL data.

E. Post-Marketing Studies

A number of recent studies were identified reporting on results from small clinical trials using the PROSIMA device. In general, it appears these studies were all smaller, of shorter duration and less well-controlled than the Ethicon-sponsored study. The results were generally similar to those described above showing variable success and frequent erosions and other adverse events. I summarize some of these studies below.

²⁹ Carey M. Higgs P. Goh J, Lim J, Leong A. Krause H. Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG. 2009 Sep;116(10):1380-6. Epub 2009 Jul 7.

1. Chen J., et al., *Prospective study on total pelvic reconstruction surgery with Prosima in the treatment of pelvic organ prolapse stage III*, Zhonghua Fu Chan Ke Za Zhi. 2012 Sep;47(9):664-8 (abstract only – study in Chinese).

Thirty-one patients with POP stage III enrolled in this prospective study from July 2010 to December 2011. No severe intraoperative complications were observed. All patients were able to recover spontaneous micturition within 5 days. Two cases experienced pelvic hematoma with diameters less than 7 cm, and resolved later. Another case had urinary tract infection. At the median follow-up 6 months (1-15 months), the rate of anatomic success defined as the leading vaginal edge above the hymen was 94% (29/31). There were significant improvements in Aa, Ba, Ap, Bp, and C ($P < 0.01$) by POP-Q. Two patients showed recurrent prolapse at 3 months and 1 year after surgery, without the need of further operation. The median score of post-operative PFIQ-7 was 0 point at 6 months and 0 point at 12 months after operation, respectively, which were significantly lower than that of 50 points pre-operation ($P < 0.01$). And there was no significant difference in the average score of PISQ-12 before and after surgery [(30 \pm 6) points versus (31 \pm 4) points] ($P > 0.05$). The rate of mesh exposure was 16% (5/31) all within 6 months and cut in clinic. There were no cases of de novo urinary incontinence and de novo dyspareunia.

2. Ching-Pei Tsai, C., Hung, M., et al., *Factors that affect early recurrence after prolapse repair by a nonanchored vaginal mesh procedure*, Taiwanese J. of Ob. & Gyn. 53 (2014) 337e342.

Fifty-two patients with symptomatic POP stage II were enrolled in this prospective study from January 2011 through to December 2011. Fifty of the 52 patients (96%) attended the 3 to 6-month postoperative assessment. Symptom and quality-of-life scores were found to have improved significantly after surgery ($p < 0.05$). Forty-two patients (84%) underwent successful treatment for POP (Stage 0-1). The other eight patients (16%) were found to have recurrent Stage 2 anterior vaginal wall prolapse, although most of them (5/8) were asymptomatic. The highest

morbidity, namely vaginal mesh exposure, occurred in four patients (8%). Investigators concluded that “Prosima seems to have limitations when used to manage severe anterior vaginal wall prolapse and concomitant surgery may further affect its effectiveness.”

3. Zhang L, et al., *Tension-free Polypropylene Mesh-related Surgical Repair for Pelvic Organ Prolapse has a Good Anatomic Success Rate but a High Risk of Complications*. Chin Med J 2015;128:295-300.

Forty-eight patients enrolled from July 2010 to July 2012. POP-Q stages were significantly improved from baseline. The two years follow-up assessment showed a 93.8% (45/48) positive anatomic outcome rate (POP-Q Stage 0, I or II without symptoms) at 12 months and 90.0% (27/30) at 24 months. Surgical repair showed better treatment for the apical and posterior compartments than the anterior at the 12- and 24-month follow-ups ($P < 0.05$). Three patients had symptomatic recurrences at 12 months after surgery; all recurrences were at the anterior compartment. Twenty-eight (58.3%) patients were satisfied with the postoperative change (PGI-C score 4 or 5), whereas seven (14.6%) patients felt disappointed (PGI-C score 1 or 2). Statistically significant improvements were observed in the symptom scores compared with those at baseline as recorded by the PFIQ-7 ($P < 0.05$). “The cumulative mesh complication rate in our study was 39.6% (19/48) during our follow-up period.” Retropubic hematoma was found in 2/48 (4.2%) patients at 48 hours after surgery, but it became asymptomatic and disappeared in seven days. Vaginal complication (C1–C3, mesh contraction or exposure) was the main complication (35.4%, 17/48), but 88.2% (15/17) of these patients were asymptomatic. Of the patients with vaginal complications, 29.4% (5/17) were clinically diagnosed over 12 months after surgery. The anterior vaginal wall was frequently involved (64.7%, 11/17). One patient complained of dyspareunia whereas the other had spontaneous pain. Patients with vaginal complications and repeated mesh exposure resolved with an exposed mesh

excision in the clinic and topical estrogen treatment. Concluding: PROSIMA related surgical repair of POP has better short-term anatomic outcomes at the apical and posterior compartments. However, this method is related to a low postoperative patient satisfaction rate and a high risk of mesh complication.

4. Wang C, Chen Z, Du G, Wang T, Yang W, et al. (2015) Outcomes of Two Different Meshes for Treatment of POP with a Concomitant Midurethral Sling for SUI: a Retrospective Cohort Study at 2 Years Postoperatively. *Int Arch Urol Complic* 1:004.

A retrospective cohort study involving 57 consecutive patients underwent either PROSIMA or AVAULTA followed by tension-free vaginal transobturator tape (TVT-O) between October 2010 and January 2012. Women who complained bothersome POP had stage II or higher prolapse of anterior vaginal wall were included. Of 57 women, 29 underwent Prosima and 28 underwent Avaulta mesh procedures. The number of success were 28 versus 26 ($P=0.53$) at 1 month and 27 versus 26 ($P=0.97$) at 2 years of Prosima and Avaulta groups, respectively. The overall and each scale scores of 3 validated questionnaires were improved significantly from baseline ($P<0.05$), but not different statistically between two groups. Complication rates did not differ significantly from two groups. PROSIMA patients experienced chronic pain (3.4%), exposure (13.8%) and urethral caruncle (3.4%). Conclusions: Both the combined procedures improved POP and concomitant SUI significantly. The efficacy and safety of the two different transvaginal meshes was promising.

IV. Expert Opinions

A. The Polypropylene Mesh in the PROSIMA Is Not Suitable As a Permanent Prosthetic Implant for Pelvic Floor Repair

Polypropylene mesh (GYNEMESH PS), like that used for the PROSIMA, has many well-known characteristics that make it unsuitable for use as a product intended for permanent

implantation in the human vaginal floor. These characteristics include the following: (1) degradation of the mesh; (2) chronic foreign body reaction; (3) infections and bio-films; (4) fibrotic bridging leading to scar plate formation; (5) mesh encapsulation and shrinkage/contraction of the encapsulated mesh; (6) deformation of the mesh; and (7) evidence that the polypropylene is incompatible with the pelvic floor and is carcinogenic.

As a result of these and other inadequacies with the mesh, and for the reasons set forth below, it is my opinion to a reasonable degree of medical certainty that the GYNEMESH PS polypropylene mesh in the PROSIMA causes a multitude of injuries, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence of POP, worsening POP, chronic dyspareunia, nerve injury of the pelvic nerves, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, Ethicon's PROSIMA mesh (GYNEMESH PS) is not suitable for its intended application as a permanent prosthetic implant for pelvic floor repair in women.

1. Polypropylene Mesh Such as GYNEMESH PS Degrades

The placement of permanent polypropylene mesh in the human vagina creates problems because of the chemical composition and structure of the mesh and the physiological conditions of the vagina and the surrounding tissues. There have been numerous studies over the last 30 years which have shown polypropylene to be chemically reactive and not inert, with flaking and fissuring demonstrated by scanning electron microscopy, which leads to degradation and release of toxic compounds into pelvic tissues. This process enhances the inflammatory and fibrotic

reactions within the tissues in the pelvic floor, causing a multitude of problems.³⁰ There have been studies suggesting that oxidation of the mesh occurs because of the polypropylene and the conditions in which it is placed.³¹ The oxidation causes the mesh to degrade, crack and break apart.³² In a recent study, 100 pelvic mesh implants were compared and over 20% showed degradation to mesh fibers.³³ In a more recent abstract, the investigators used a scanning electron microscope, an atomic force microscope and Raman spectroscopy to examine a number of meshes explanted due to complications after 4-7 years in the pelvic floor.³⁴ When compared to “pristine samples,” the study “revealed extensive surface degradation with formation of microscopic surface cracks” and that the “surface roughness of the explant samples was increased by several orders of magnitude” for all of the polypropylene meshes.³⁵

Because of the structural complexities of the vagina and the nature of the chemicals ordinarily found in the vagina and its surrounding tissues, there are several reasons why polypropylene presents unique problems when placed in the vagina. An Engineering Bulletin from Propex, entitled “*EB-405, The Durability of Polypropylene Geotextiles for Waste Containment Application*,” from 2011, states that, “[P]olypropylene is vulnerable to the following substances: highly oxidized substances such as (peroxide), certain chlorinated hydrocarbons (halogenated hydrocarbons), and certain aromatic hydrocarbons.”³⁶ It is well

³⁰ Coda A., *Hernia* (2003);7:29; Jongebloed, WL, “*Degradation of Polypropylene in the Human Eye: A SEM Study*,” Doc. Ophthalmol., 1986 64 (1:143-152); Skrypunch, O.W., “*Giant Papillary Conjunctivitis from an Exposed Prolene Suture*,” Can. J Ophthalmology, 1986 21:(5: 189-192).

³¹ Costello C., et al., “*Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants from a Single Patient*,” Surgical Innovation , (2007), 143:168- 176.

³² *Id.*

³³ Clavé A, Yahi H, Hammou JC, Montanari S, Gounon P, Clavé H, “*Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*,” J Biomed Mater Res B Appl Biomater, 2007, Oct 83(1:44-9).

³⁴ Tzartzeva K, Lingam D, et al., IN-DEPTH NANO-INVESTIGATION OF VAGINAL MESH AND TAPE FIBER EXPLANTS IN WOMEN.

³⁵ *Id.* (“The results of this study point to significant physical degradation of the meshes for all those implanted for several years”).

³⁶ Citing Schneider H., *Long Term Performance of Polypropylene Geosynthetics, "Durability and Aging of*

known to physicians with expertise in the pelvic floor that vaginal and perivaginal tissues are ready sources for peroxide. The vaginal species lactobacillus produces hydrogen peroxide and lactic acid from collagen that is produced in the squamous cells of the vagina. Estrogen is the catalyst for the production of collagen from the vaginal cells. It is also well known that hydrogen peroxide produced by the lactobacillus species is important in controlling the vaginal micro-flora.³⁷ It is also known that aromatic hydrocarbons can be found in adipose tissues³⁸ and in the blood stream.³⁹ Accordingly, the body location where the polypropylene mesh is being placed can expose it to known chemical degradation agents.

However, chemical degradation is not the only way that polypropylene degrades *in vivo*. Bacteria such as Pseudomonas species, Bacillus species, Mycobacterium and Corynebacterium species, which are present in a woman's vagina, can degrade petroleum hydrocarbons.⁴⁰ Also fungi such as the Candida species, also present, can degrade petroleum-based hydrocarbons.⁴¹ Microbial agents that can be found inside the normal and abnormal flora of the human vagina such as Candida and, with certain pelvic infections such as Bacillus and Pseudomonas, can be a source of biological degradation of polypropylene products.

Geosynthetics, Koerner, RM, Ed., (Elsevier 1989) 95-109.

³⁷ Strus, M., et al., *The In Vitro Effect of Hydrogen Peroxide in Vaginal Microbial Communities*, FEMS Immunol Med Microbiol, 2006 Oct; 48(1:56-63) ("Hydrogen Peroxide reached concentrations of from 0.05 to 1.0 mm, which under intensive aeration increases even up to 1.8 mm."); Strus, M., "Hydrogen Peroxide Produced by Lactobacillus Species as a Regulatory Molecule for Vaginal Micro-flora," Med Dosw Mikrobiol, 2004: 56(1:67-77).

³⁸ Moon, HB., "Occurrence and Accumulation Patterns of Polycyclic Aromatic Hydrocarbons and Synthetic Musk Compounds in Adipose Tissues of Korean Females," Chemosphere 2012 (86:485-490), these aromatic hydrocarbons were noted to be present in, "[t]otal concentrations of PAHs and SMCs in adipose tissues rang[ing] from 15 to 361 (mean:119) ngg(-1) lipid weight and from 38 to 253 (mean:106) nng(-1) lipid weight respectively.... The results of this study provide baseline information on exposure of PAHs and SMCs to the general population in Koreans.").

³⁹ "Determination of Volatile Purgeable Halogenated Hydrocarbon in Human Adipose Tissue and Blood Stream," Bulletin of Environmental Contamination and Toxicology, Volume 23, Issue 1, at 244-49 (1979) (found halogenated hydrocarbons, pesticide by-products, both in human adipose tissues and the blood stream); Anderson, H., "Utilization of Adipose Tissue Biopsy and Characterizing Human Halogenated Hydrocarbon Exposure," Environmental Health Perspectives, Volume 60, at 127-131 (1985).

⁴⁰ Das, N., "Review Article: Microbial Degradation of Petroleum Hydrocarbons Contaminant: An Overview", Journal of Biotechnology Research International, Volume 2011, Article ID 941810.

⁴¹ Das, N., et al., *Review Article: Microbial Degradation of Petroleum Hydrocarbon Contaminants: an Overview*, J Biotech Res Intl, 2011, Article ID 941810, 1-13.

A paper entitled, “Health, Safety and Environment Fact Sheet: Hazardous Substances - Plastics,” from CAW/TCA (www.caw.ca), August 2011:343, found that polypropylene degradation products and residues can form carbon monoxide, acrolein, aldehydes and acids, qualifying these health hazards as toxic and irritants. In a paper from D Lithner in 2011 at 4, entitled, “Environmental and Health Hazards of Chemicals in Plastic Polymers and Products,” University of Gothenburg, it is stated that, “[n]on-biodegradable polymers can be degraded by heat, oxidation, light, ionic radiation, hydrolysis and mechanical shear, and by pollutants such as carbon monoxide, sulphur dioxide, nitrogen oxide and ozone. This causes the polymer to get brittle, to fragment into small pieces and to release degradation products.” (Citations omitted.) Lithner continues, “[o]ther substances (besides monomers) are often needed for polymerization to occur, for instance initiators, catalysts, and, depending on manufacturing process, solvents may also be used. The resulting plastic polymer can be blended with different additives, for instance plasticizers, flame retardants, heat stabilizers, antioxidants, light stabilizers, lubricants, acid scavengers, antimicrobial agents, anti-static agents, pigments, blowing agents and fillers, and is finally processed into a plastic product. There are many different plastic polymers and several thousand different additives, which result in an extremely large variation in chemical composition of plastic products.” Id. at 6 (citations omitted). “Since plastic products are composed of many different chemicals, and the main part of these [are] broken down into something completely different; this complicates the prediction.” Id. at 8. “The type and quantity of degradation products formed may also be influenced by degradation mechanisms, presence of polymerization impurities, and surrounding factors, e.g. temperature and oxygen. Id. at 9. “Few studies combining leaching tests with toxicity tests have been performed on plastic products.” Id. at 12. The available peer-reviewed literature regarding degradation/oxidation of polypropylene in

the human body dates back to the 1960's and has been reported in numerous such publications.⁴²

Two of the more important and salient articles regarding reported degradation in explanted surgical meshes (hernia and pelvic floor) are the Costello and Clave articles. In his paper, "*Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Implants from a Single Patient*," Prof. C Costello reported that hernia mesh made of polypropylene oxidized and degraded as a result of the metabolites produced by phagocytic cells during the body's inflammatory reaction to the mesh. High-magnification photographs showed cracking and peeling of the polypropylene fibers. Ethicon referenced this article in internal emails.⁴³

Another article by A Clave, "*Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*," also displayed high magnification photos of polypropylene fibers from explanted meshes and, in this case, the meshes were explanted from women's pelvic floor tissue.⁴⁴ The heavyweight meshes showed even greater cracking than the lower density meshes, but according to Prof/Dr. Clave, ALL 84 of the polypropylene explants examined showed degradation. Oxidation of the implanted mesh due to free radical attack through the synthesis of peroxides, superoxides and hypochlorous acid during the chronic inflammatory phase was listed as just one potential cause for the oxidative degradation within the "septic environment" in which the pelvic meshes are placed.

Given the information available to Ethicon in the scientific and medical literature concerning the potential for degradation of polypropylene, it is my opinion to a reasonable degree of medical certainty that Ethicon should have conducted clinically relevant testing to

⁴² Liebert, T, et al., *Subcutaneous Implants of Polypropylene Filaments*, J Biomed Mater Res. 1976 (10:939-951); Williams, D., *Review of Biodegradation of Surgical Polymers*, J Materials Sci, 1982 (17:1233-1246); Oswald, H.J., et al., *The Deterioration of Polypropylene By Oxidative Degradation*, Polymer Eng Sci, 1965 (5:152-158).

⁴³ ETH.MESH.005588123.

⁴⁴ Clave, A., *Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*, I Urogynecol J 2010 21:261-270.

determine if naturally occurring conditions in the vagina could cause polypropylene to degrade and if so, what the quantity and quality of the products of degradation would be, whether they would be released into surrounding tissues and/or migrate in the woman's body, what the clinical implications for the woman would be and whether some women's bodies would react differently to the mesh and degradative process and its by-products.

Ethicon's Daniel Burkley, a Principal Scientist at Ethicon, testified that the science supported the conclusion that mesh could shrink, contract and degrade. Specifically, Mr. Burkley agreed that the risk of degradation increases when you have a severe inflammatory response with mesh implanted in a contaminated field.⁴⁵ Mr. Burkley also testified that polypropylene mesh in human beings is subject to some slight degree of surface degradation.⁴⁶ He agreed that degradation might be better understood if Ethicon studied or tested a product that is permanently implanted in women.⁴⁷ In fact, according to Mr. Burkley, Ethicon only conducted one study related to degradation and Prolene material. This study consisted of a Prolene suture implanted into dogs.⁴⁸ Mr. Burkley testified that the study and photos from the dog actually showed that the Prolene material used in TVT degraded and was still degrading after 7 years.⁴⁹

It is now clear from Ethicon's internal documents that Mr. Burkley was incorrect when he said that Ethicon only performed one study related to degradation of Prolene. Contrary to Mr. Burkley's claim, he and other Ethicon scientists were involved in a Prolene human explant study that was conducted in 1987 which found that Prolene degrades while in the body. According to Ethicon's documents, Ethicon's scientists received 58 Prolene human explants from Professor

⁴⁵ Burkley Dep. (5/22/13) 184:17-24.

⁴⁶ Burkley Dep. (5/22/13) 206:2-11

⁴⁷ Burkley Dep. (5/22/13) 206:12-25.

⁴⁸ ETH.MESH.05453719 (Seven year data for ten year Prolene study: ERF 85-219).

⁴⁹ Burkley Dep. (5/23/13) 315:8-13.

Robert Guidon⁵⁰ which were analyzed by Ethicon's scientists using scanning electron microscopy ("SEM"). The SEM study revealed that 34 of the 58 Prolene explants (58%) were cracked. Further studies, including FTIR and melt point analysis, were conducted by Ethicon's scientists to determine the cause of the cracking observed in Prof. Guidon's explants. In a report authored by Mr. Burkley on September 30, 1987, he concluded that the Prolene explants had insufficient antioxidants to protect them from oxidation which led to *in vivo* degradation of the Prolene devices.⁵¹ Importantly, Ethicon has not made any changes to Prolene since it was introduced to the market, except that, in 2011, they reduced the amount of Sanatanox (another antioxidant), which could potentially make Prolene more, not less, susceptible to oxidized degradation.⁵² Thus, Ethicon's internal studies clearly demonstrate that Ethicon's scientists had concluded that Prolene can degrade while implanted in the human body.

Ethicon subsequently hired an outside consulting firm to resolve the cause of the erosion of its surgical meshes for the pelvic floor. In a June 22, 2011, report, PA Consulting Group informed Ethicon that, "[p]olypropylene can suffer from degradation following implant... a process which initiates after a few days post implantation in animal studies."⁵³ The consulting report discusses numerous images of polypropylene mesh that show "physical degradation" of the mesh.⁵⁴ In addition, in a 2009 presentation, Ethicon Medical Director Piet Hinoul stated that meshes are not biologically inert.⁵⁵

I have personally seen mesh that is broken, cracked, brittle and looks different from when

⁵⁰ DEPO.ETH.MESH.00004755

⁵¹ ETH.MESH.12831391 at ETH.MESH.1281392

⁵² ETH.MESH.02589032 and ETH.MESH.07192929 (May 18, 2011 PA Consulting Report: Investigating Mesh Erosion in Pelvic Floor Repair and PowerPoint presentations)

⁵³ ETH.MESH.02589032 and ETH.MESH.07192929 (May 18, 2011 PA Consulting Report: Investigating Mesh Erosion in Pelvic Floor Repair and PowerPoint presentation).

⁵⁴ *Id.*

⁵⁵ ETH.MESH.01264260 (Presentation, "Prolift+M," P Hinoul, MD, Ethicon Pelvic Floor Expert's Meeting – Nederland, Utrecht, May 7, 2009).

it came out of the package. Interestingly, despite years of scientific literature, its own internal dog study, a report performed by consultants it hired, showing that degradation of mesh occurs, and even despite the fact that Ethicon's own internal risk assessments include degradation as a known risk, Ethicon's Instructions for Use (IFU) claimed that the mesh in the PROSIMA "is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes."⁵⁶ This is not simply inaccurate, but is false and misleading for all of the reasons stated above, including, most importantly, that Ethicon's own internal documents and testimony from its employees confirm that the mesh degrades.

It is my opinion to a reasonable degree of medical certainty that the mesh used in PROSIMA degrades. The effect of chemical and biological degradation of the GYNEMESH PS in a woman's tissues can lead to a greater foreign body reaction, enhanced inflammatory response and excessive scarring, which can lead to increased degradation and severe complications in patients, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening POP, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, impaired immune system, injury to the vaginal wall, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's PROSIMA is not suitable for its intended application as a permanent prosthetic implant for pelvic floor repair in women.

Given the information available in the scientific and medical literature concerning the potential for degradation of polypropylene, it is my opinion to a reasonable degree of medical certainty that Ethicon should have conducted clinically relevant testing to determine if naturally occurring conditions in the vagina could cause polypropylene to degrade and if so, what the

⁵⁶ PROSIMA IFU ETH.MESH.02341398.

quantity and quality of the products of degradation would be, whether they would be released into surrounding tissues and/or migrate in the woman's body, what the clinical implications for the woman would be and whether some women's body's would react differently to the mesh and the degradative process and its by-products.

Moreover, Ethicon failed to inform physicians or patients about the potential for degradation of the mesh and the complications that could follow. In fact, Ethicon not only failed to disclose these risks to physicians and patients, it did not accurately describe these significant risks by calling them "transitory" and by putting inaccurate statements about degradation in its IFU. This is information physicians need to know in order to have a fair and proper conversation with their patients about the use of a product. In addition, it is important for physicians to have this information when their patients present with complications from their mesh implant. Physicians rely on device manufacturers to inform them of the risks and complications associated with their products instead of downplaying them or inaccurately stating them. By not disclosing this safety information to physicians and their patients, it is my opinion to a reasonable degree of medical certainty that Ethicon failed to properly inform physicians and patients about the risks of degradation of GYNEMESH PS in the PROSIMA. In addition, by failing to inform physicians, Ethicon did not provide them with an opportunity to adequately discuss these risks with their patients.

2. Polypropylene Mesh Causes Chronic Foreign Body Response

The human body has a natural and fairly predictable "host defense response" to any foreign object placed inside of it. Whether a splinter or a surgical mesh, the human body will send white blood cells to attack the invader and, if the products of inflammation cannot ward off or destroy the invader, including if the invader is anything from bacteria to prosthetic implants, the initial acute inflammatory phase is followed by a chronic inflammatory phase. Therefore,

with the placement of something like a permanent surgical mesh in human tissues, there will be a chronic or permanent foreign body reaction to the implant, as well as a chronic inflammatory response by the body.⁵⁷ In fact, Ethicon Medical Directors, Piet Hinoul and Charlotte Owens, have both testified that the chronic foreign body reaction created by the body's response to mesh can cause a severe inflammatory reaction, which can cause chronic pain, nerve entrapment, erosions, dyspareunia and the need for additional surgeries.⁵⁸

Consultants and experts in the field informed Ethicon that there would be chronic tissue reaction to its polypropylene meshes. During a 2006 meeting at one of Ethicon's facilities, Bernd Klosterhalfen, a pathology consultant expert for Ethicon, informed Ethicon that there can be a continuing reaction between tissues in the body and mesh for up to 20 years.⁵⁹ In addition, during a February 2007 meeting, Ethicon stated that there can be, "[E]xcessive FBR [foreign body reaction]> massive scar plate > more shrinkage."⁶⁰

Internally, Ethicon's scientists agreed. Dr. Holste testified that chronic foreign body reactions occur in Ethicon's small pore, heavyweight meshes like the GYNEMESH PS mesh found in PROSIMA.⁶¹ In fact, Dr. Holste testified that Ethicon developed lighter weight, large pore meshes in order to minimize the complications seen with heavyweight meshes like the GYNEMESH PS used in PROSIMA.⁶² Ethicon employee, Christophe Vailhe, testified that there can be an excessive inflammatory reaction or foreign body reaction that would lead to mesh

⁵⁷ Klinge, U., et al., *Shrinking of Polypropylene Mesh In Vivo: An Experimental Study in Dogs*, Eur J Surg 1998, 164: 965-969; Klinge, U., *Foreign Body reaction to Meshes Used for the Repair of Abdominal Wall Hernias*, Eur J Surg 1998, 164:951-960; Klosterhalfen, B., *The lightweight and large porous mesh concept for hernia repair*, Expert Rev. Med. Devices 2005, 2(1); Binnebosel M, et al., *Biocompatibility of prosthetic meshes in abdominal surgery*, Semin Immunopathol 2011, 33:235-243; ETH.MESH.03658577 (Biocompatibility of Ultrapro).

⁵⁸ Hinoul Dep. (4/5/12) 99:09-25; (4/6/12) 518:14-520:20; (6/26/13) 175:1-176:17; 184:18-22; 328:10-24; Owens Dep. (9/12/2012) 98:11-99:07.

⁵⁹ ETH.MESH.00870466 (June 6, 2006 Ethicon Expert Meeting Meshes for Pelvic Floor Repair, Norderstedt).

⁶⁰ ETH.MESH.01218361 (Ethicon Presentation: "State of Knowledge in 'mesh shrinkage' -What do we know").

⁶¹ Holste Dep. (7/29/13) 52:5-55:21.

⁶² Holste Dep. (7/29/13) 51:3-53:6.

erosion and contraction.⁶³

Contrary to this scientific evidence, Ethicon informed doctors in its IFU that its PROSIMA mesh was “nonreactive” and “elicits a minimal to slight inflammatory reaction, which is transient.”⁶⁴ This was despite all of the internal documents and testimony discussed above from Ethicon’s Medical Affairs and Research and Development employees that chronic foreign body reaction occurs in small pore, heavyweight meshes like the mesh in PROSIMA. Moreover, as one of Ethicon’s lead engineers stated: “the foreign body reaction is not transitory – it doesn’t ever go away, but decreases over time to a minimal level.”⁶⁵ That is, it is chronic. I have reviewed numerous pathology reports from my own patients and other physician’s patients and pathology reports reviewed in litigations describing foreign body reactions. Hence, the mesh potentiates a chronic, long-term inflammation. This is contrary to the express language of the PROSIMA IFU.

For the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the polypropylene mesh in the PROSIMA creates a chronic foreign body reaction which can lead to severe complications in patients, including the possibility of multiple erosions that can occur throughout one’s lifetime, chronic and debilitating pelvic pain, POP recurrence, worsening POP, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to the vaginal walls, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon’s PROSIMA mesh is not suitable for its intended application as a permanent prosthetic implant for pelvic floor

⁶³ Vailhe Dep. (6/21/13) 383:8-19.

⁶⁴ Interestingly, the “transient” language was removed from other Ethicon Prolene mesh IFUs in 2010 – but was still in the PROSIMA IFU. ETH.MESH.02340406; ETH.MESH.02340531; TVT IFU, May 2015

⁶⁵ ETH.MESH.00211259.

repair in women.

Moreover, Ethicon failed to inform physicians or patients about the potential for a severe, chronic foreign body response and the complications that could follow. In fact, not only did Ethicon fail to disclose these risks, it mischaracterized the risks by calling them “transient” and by putting inaccurate statements about inflammatory response in its IFU. This is information physicians need to know in order to have a fair and proper conversation with their patients about the use of a product. In addition, physicians require this information to properly assess and treat a patient who presents with complications from a vaginal mesh. Physicians rely on device manufacturers to inform them of the risks and complications associated with its products instead of downplaying them or inaccurately stating them. By not disclosing this safety information to physicians and their patients, it is my opinion to a reasonable degree of medical certainty that Ethicon failed to properly inform physicians and patients about the risks of foreign body response of the mesh in the PROSIMA. In addition, by failing to inform physicians, Ethicon did not provide them with an opportunity to adequately discuss these risks with their patients or to properly assess and treat women who experienced adverse events from the mesh.

3. Polypropylene Mesh Such as GYNEMESH PS Causes and Perpetuates Infections

The placement of pelvic floor meshes, including PROSIMA, violates one of the most basic tenets of surgical teachings in that it is the placement of a permanent implant into the patient through a “clean contaminated” surgical field, *i.e.* the vagina, which is not sterile and can never be completely sterilized.

In PROSIMA, the weave of the mesh produces very small interstices which allow bacteria to enter and to hide from the host defenses designed to eliminate them. The bacteria can secrete encasing polysaccharide slime (biofilm), which further serves to shield the bacteria from

destruction by white blood cells and macrophages.⁶⁶ The effect and consequences of biofilm is to increase the foreign body reaction, resulting in chronic infections, chronic inflammation, erosions, and mesh and scar contracture as confirmed by the testimony of Ethicon's Head of Pre-Clinical, Dr. Joerg Holste.⁶⁷

Importantly, the biofilm actually serves as a protection for the bacteria surrounding the mesh fibers against the body's host defense response (white blood cells), which are intended to destroy foreign invaders like bacteria. Thus, the weave induces the creation of a shield against the body's defenses to the bacteria encased in the woven mesh, inhibiting the body's ability to fight off the infective agents within the mesh. The large surface area promotes wicking of fluids and bacteria which provides a safe haven for bacteria which attach themselves to the mesh during the insertion process.⁶⁸ Daniel Burkley testified that reducing surface area could reduce the amount of chronic inflammation.⁶⁹ Additionally, the size of the mesh placed equates to a large surface area with many places for bacteria to hide while being protected from host defenses leading to numerous complications.⁷⁰

There have been numerous peer-reviewed journal articles regarding secondary-mesh related infections as well as the dangers of implanting surgical mesh in a clean/contaminated field. Of note, in May of 2013, at the AUA meeting in San Diego, Dr. Shah and his colleagues reported on the "*Bacteriological Analysis of Explanted Transvaginal Meshes*," which included

⁶⁶ Osterberg, B., et al., *Effect of Suture Materials on Bacterial Survival in Infected Wounds: An Experimental Study*, Acta. Chir. Scand 1979, 145:7 431-434; Merritt, K., *Factors Influencing Bacterial Adherence to Biomaterials*, J Biomat Appl 1991, 5:185-203; An, Y., *Concise Review of Mechanisms of Bacterial Adhesion to Biomaterial Surfaces*, J Biomed Mater Res (Appl Biomat) 1998, 43:338-348; The TVM Group: J. Berrocal, et al., *Conceptual advances in the surgical management of genital prolapsed*, J Gynecol Obstet Biol Reprod 2004, 33:577-587.

⁶⁷ Holste Dep. (7/30/13) 295:24-298:14, 411:15-414:24.

⁶⁸ Klinge, U., et al., *Do Multifilament Alloplastic Meshes Increase the Infection Rate? Analysis of the Polymeric Surface, the Bacteria Adherence, and the In Vivo Consequences in a Rat Model*, J Biomed Mater Res 2002, 63:765-771; Vollebregt, A., et al., *Bacterial Colonisation of Collagen-Coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?*, Int Urogyn J 2009, 20:1345-51.

⁶⁹ Burkley Dep. (5/22/13) 371.

⁷⁰ Klinge, *supra* n. 26; Vollebregt, *supra* n. 26.

explanted samples of both SUI slings and prolapse meshes. Of the 50 explants examined, 52% of those explanted due to patient complaints of painful mesh were infused with pathogenic organisms, 20% of those explanted due to vaginal erosions had pathogenic organism, and 83% of those explanted due to urinary tract erosions were contaminated with pathogenic organisms.⁷¹

When polypropylene particles separate from the surface of the mesh fiber due to degradation, see *infra*, or particle loss or fraying, the surface area of the mesh is greatly increased thus providing even greater areas for bacterial adherence to the mesh, more elution of toxic compounds from the polypropylene, and also more of the free toxic polypropylene itself, all of which increases the inflammatory reaction and intensity of the fibrosis.⁷² This cracking of the mesh surface also provides safe harbors for infectious bacteria to proliferate.

In his periodic histopathological analyses for Ethicon of its pelvic floor explants, Dr. Klosterhalfen reported to Ethicon that, in virtually 100% of those instances in which mesh had been explanted due to erosions, he found a secondary, mesh-related infection at the tissue/mesh interface.⁷³ Mesh exposure and erosion cause the fibers to be further exposed to bacteria that will adhere to and colonize on the mesh surface.

Ethicon never performed any long-term, clinical studies to determine whether the warnings given to them through the peer-reviewed literature and by their own experts and consultants were accurate, namely that mesh-related infections are real; that they cause patient injury in the form mesh erosions, pain syndromes and recurrent, late infections.

Therefore, it is my opinion to a reasonable degree of medical certainty that the PROSIMA mesh is susceptible to biofilm formation due to the weave of the mesh allowing the

⁷¹ Shah, K., et al., Bacteriological Analysis of Explanted Transvaginal Meshes (Abstract 1144).

⁷² Jongebloed, *supra*, n. 1; Sternschuss, G, et al., *Post-Implantation Alterations of Polypropylene in the Human*, J Urol 2012, 188:27-32; Clave, *supra*, at 6.

⁷³ ETH.MESH.00006636.

infiltration, harboring, and protection of bacterial contaminants; the degraded mesh surface harboring bacteria; the passage through and into a clean/contaminated field; and after exposure/erosion of the mesh into the vagina or other organs, further contamination of the mesh with a multitude of vaginal flora that further increases the risk of harmful and recurrent infections in women.

Accordingly, the PROSIMA transvaginal technique, as well as the PROSIMA mesh itself, are not safe for their intended purpose of implantation into a woman's pelvic tissues and can lead to severe complications in patients, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening POP, de novo incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to the vaginal wall, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's PROSIMA mesh is not suitable for its intended application as a permanent prosthetic implant for pelvic floor repair in women.

4. GYNEMESH PS Is a Small-Pore, Heavyweight Mesh that Promotes Fibrotic Bridging and Scar-Plate Formation

Fibrotic bridging occurs when the fibers surrounding the pores of the mesh are too close together to allow the tissue in the pore enough room to recover from the trauma of tissue damage due to implanting a surgical prosthetic device. Pores that are large enough for good, newly-vascularized tissue tend to be filled with fatty tissue versus small pores that become filled with scarred or fibrotic tissue. In those instances, the scar forms across the pores or "bridges" from one side of the pore to the other. This can occur either due to the granulomas around the mesh fibers joining together or due to densely-formed fibroblasts between these granulomas. Either

way, such bridging can lead to the creation of a rigid, scar plate that can encapsulate the mesh with scar tissue. Simply put, small mesh pores that cause fibrotic bridging turn the mesh into a solid sheet of scar tissue and there is no space or room for tissue to grow into the mesh, which is contrary to the intended purpose of the mesh. The fibrotic bridging and scar plate prevents tissue in-growth and causes complications, including, among other things, pain with the rigid mesh, shrinkage or contraction of the mesh, erosions due to mechanical irritation in the tissue of a rigid, scar-plated mesh, nerve entrapment, chronic pain and dyspareunia. This concept is best illustrated by a DVD produced by Ethicon which features an Ethicon consultant, Dr. Todd Heniford, talking about a heavyweight, small pore mesh called Marlex used for hernia repairs.⁷⁴

The mesh used in PROSIMA is of heavyweight, small pore construction. Ethicon Scientists have acknowledged that the Marlex mesh in the video is similar to the GYNEMESH PS in TVT in that is heavy weight small pore mesh.⁷⁵ Ethicon has also relied on the works of Dr. Heniford relating to lightweight mesh and cited to his works in their marketing materials and professional educational materials for pelvic mesh products. Moreover, Ethicon relied on science and information regarding hernia meshes to claim the safety and efficacy of their pelvic mesh products to regulatory bodies. At least one medical director at Ethicon, Dr. Thomas Divilio, has described the work done by Dr. Heniford and others as “material science” that would apply to both hernia and pelvic mesh products. In my opinion this video, as well as other science and information regarding hernia meshes and other pelvic meshes, is of particular relevance when discussing the PROSIMA mesh as Ethicon chose to move to large pore, light weight meshes in these other areas, but not for PROSIMA. In fact, prior to the launch of PROSIMA, Ethicon

⁷⁴ Heniford, B.T., 2007, *The benefits of lightweight meshes in Ventral Hernia Repair in Ventral Hernia Repair*, Video produced by Ethicon.

⁷⁵ ETH.MESH.05918776 (5/04/04 Email from Schiaparelli, Jill, Strategic Grown Subject: Marlex Experience); Batke Dep. (8/01/13) 87:12 - 88:10, 113:3-114:3, 257:23-259:13; Holste Dep (7/29/13) 51:3-53:6, 55:22-57:4; Vailhe Dep. (6/20/13) 182:2 185:5.

considered using lighter weight, absorbable GYNEMESH+M in the device but chose not to as it would delay commercialization of the product.⁷⁶

In the video, Dr. Heniford talks about the dangers of heavy weight, small pore meshes.⁷⁷ In fact, Dr. Heniford states, “there is no excuse for using heavy weight, small pore meshes in the human body.”⁷⁸ I have explanted numerous meshes and have witnessed meshes with extensive scar plating and mesh encapsulation similar to the hardened/stiffened mesh viewed in the Heniford video. In numerous emails, Ethicon employees discussed concerns regarding fibrotic bridging.⁷⁹ They have testified that the heavy weight, small pore type of mesh in the PROSIMA can lead to an increased risk of foreign body reaction, contraction of the mesh, nerve entrapment, erosions and chronic pelvic pain.⁸⁰

In other emails, when discussing these concepts, Ethicon’s World Wide Marketing Director for General Surgery, Marty Chomiak, states that “we want to avoid ‘bridging’, therefore we think large pores are better than small....”⁸¹ Ethicon also had information and scientific knowledge regarding superior mesh designs to prevent fibrotic bridging and scar plating. Specifically, Ethicon also had scientific knowledge that light weight, large pore mesh could decrease the likelihood of foreign body reaction, fibrotic bridging and scar plating.⁸²

⁷⁶ ETH.MESH.00008631.

⁷⁷ Heniford Video, *supra*, n. 46.

⁷⁸ *Id.*

⁷⁹ ETH.MESH.04037600 (Innovations in mesh development); ETH.MESH.05920616 (7/20/07 ; Emails from Chomiak, M. to Batke, B., et al. re Defining light weight mesh); ETH.MESH.05585033 (Boris Batke Presentation – Project Edelweis – Ultrapro); ETH.MESH.05446127 (3/13/2006 Emails from Holste, J. to Engel, D., et al. re Mesh and Tissue Contraction in Animal – “Shrinking Meshes?”); ETH.MESH.05475773 (2/09/2007 Boris Batke, Ethicon R&D, Presentation: *The (clinical) argument of lightweight mesh in abdominal surgery*); ETH.MESH.04015102 (3/1/12 Email from Batke, Boris to Mayes, C. re AGES Pelvic Floor Conference-Gala Dinner Invitation); ETH.MESH.04037600 (3/15/12 Boris, B. PowerPoint Presentation, *Innovations in Mesh Development*, Melbourne AGES 2012).

⁸⁰ Batke Dep. (8/1/13) 87:12-88:10, 113:3-114:3, 257:23-259:13; Holste Dep. (7/29/13) 51:3-53:6, 55:22-57:4; Vailhe Dep. (6/20/13) 182:2-185:5.

⁸¹ ETH.MESH.05920616 (7/20/07 Email from Chomiak, M. re Defining Light Weight Mesh).

⁸² Batke Dep. (8/1/13) 87:12-88:10, 113:3-114:3, 257:23-259:13; Holste (7/29/13) 51:3 - 53:6, 55:22 - 57:4; Vailhe Dep. (6/20/13) 182:2-185:5.

Liang et al who compared the effects of GyneMesh PS to two lower weight, higher porosity, less stiff meshes following implantation into a primate vagina rather than a Rat back. This study, which was sponsored by the NIH, found “Following implantation with the heavier, less porous, and stiffer mesh, Gynemesh PS, the degradation of vaginal collagen and elastin exceeded synthesis, most likely as a result of increased activity of MMPs, resulting in a structurally compromised tissue”⁸³

Despite having clinical knowledge of the importance of pore size to successful outcomes, and dozens of emails about the importance of pore size, Ethicon’s acknowledged that, “Pore size in microns was not measured during the development of the Prolene Soft Mesh.”⁸⁴

In addition, the pore size of a mesh can change when the mesh is put under stress such as when the mesh is tensioned. Dan Smith agreed that these stresses can make an effective pore size smaller than 1 mm.

Q. You would agree, Mr. Smith, that if the measurement across the pores we’re looking at here – let’s assume you measure across one of those pores and let’s say it’s more -- let’s say it’s 1 millimeter across hypothetically. If a load is put on the mesh and it changes the pore size, that pore could be, after a load is put on it, under 1 millimeter; correct?

A: It’s possible depending on the load.⁸⁵

Ethicon engineer Christophe Vaihle testified that “excessive tension on the mesh would lead to the decrease in pore size that can lead to poor tissue integration....”⁸⁶ Ethicon used the older GYNEMESH PS despite what Ethicon considers to be “revolutionary” advancements in polypropylene mesh design that it brought to other pelvic floor polypropylene mesh products.⁸⁷

⁸³ Liang, Rui, Wenjun Zong, Stacy Palcsey, Steven Abramowitch, and Pamela A. Moalli. “Impact of Prolapse Meshes on the Metabolism of Vaginal Extracellular Matrix in Rhesus Macaque.” *Obstetrical & Gynecological Survey*, 70.6 (2015): 385-87.

⁸⁴ ETH.MESH.01431617.

⁸⁵ Smith Dep. (2/3/2014) 816:5 to 816:15.

⁸⁶ Vailhe Dep., (6/20/13) 224:10-226:21.

⁸⁷ ETH.MESH.03905968; *see also* Prolift +M CER (“As the mass of a mesh implant is reduced and the pore size is increased, the surface area exposed to the host is reduced, and the foreign body reaction to the implant is

In summary, for the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the polypropylene mesh in the PROSIMA causes fibrotic bridging in the body, resulting in an increased inflammatory response leading to a multitude of injuries, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening POP, de novo incontinence, dyspareunia that can be chronic, nerve injury, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to vaginal walls, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's PROSIMA is not suitable for its intended application as a permanent prosthetic implant for pelvic floor repair in women.

Moreover, Ethicon did not inform physicians and patients that its mesh was susceptible to fibrotic bridging. Ethicon failed to warn physicians and patients that fibrotic bridging could occur leading to painful erosions, recurrent, late infections, nerve injury and the need for mesh removal. By failing to do so, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity adequately to discuss these risks with their patients. Moreover, Ethicon failed to provide sufficient information for physicians to adequately assess and treat patients who presented with mesh-related complications – for example, Ethicon failed to provide any guidance or information of the proper methods to remove mesh that had formed a hard scar-plate without inflicting further injury on the patients.

5. Polypropylene Meshes, Including PROSIMA'S GYNEMESH PS, Contract and Shrink

Mesh contracture or shrinkage is an event that takes place after the implantation of mesh and relates to the wound healing process that occurs after the surgical trauma of implanting a

reduced.”).

foreign body made of polypropylene in the sensitive tissues of the vagina and pelvis. By 1998, polypropylene mesh was known to contract or shrink 30-50%.⁸⁸ These findings were later confirmed in numerous papers, such as those by W. Cobb and his colleagues – one of whom was Dr. Heniford (referenced above).⁸⁹ This also showed that heavier weight meshes like GYNEMESH PS led to greater amounts of contraction. Contraction or shrinkage is closely related to the pore size and weight of the mesh. Small pore, heavy weight mesh leads to fibrotic bridging which leads to scar plates, mesh encapsulation and shrinkage or contraction of the mesh, which is compounded by the shrinkage effect associated with the normal wound healing process already occurring in the tissue. These adverse consequences often do not resolve upon removal of the mesh.⁹⁰

This phenomenon of shrinkage and its relation to the design of the pores as well as the consequences to the patient were illustrated by Ethicon Scientist Joerge Holste in a March 13, 2006, email discussing a paper he authored entitled “Shrinking Meshes?”⁹¹ In his email, Dr. Holste states “this was our scientific statement on mesh shrinkage: Basically, small pores, heavy weight meshes induce more fibrotic bridging tissue reaction causing more mesh shrinkage during maturation of the collagenous tissue.”⁹² In addition, in a presentation by Boris Batke, Associate Director R&D, he states heavier-weight polypropylene mesh results in mesh contraction of 33%.⁹³ In an email dated November of 2002, related to a discussion of mesh used in a TVT product, Axel Arnaud, one of Ethicon’s medical directors, used 30% shrinkage of the mesh as a

⁸⁸ Klinge, U, *Shrinking of Polypropelen Mesh in Vivo: An Experimental Study in Dogs*, Eur J Surg 1998, 164:965-969.

⁸⁹ Cobb, W., et al., *The Argument for Lightweight Polypropylene Mesh in Hernia Repair*, Surgical Innovation 2005, 12(1):T1-T7.

⁹⁰ Feiner B., Maher C., *Vaginal mesh contraction: definition, clinical presentation, and management*. Obstet. Gynecol (2010 Feb); 115(2 Pt 1):325-30.

⁹¹ ETH.MESH 05446127.

⁹² *Id.*

⁹³ ETH.MESH 05479717 (3/1/11 Boris Batke, Ethicon Associate Director R&D, Presentation: Ethicon Polypropylene Mesh Technology).

“rule of thumb.”⁹⁴ At an Ethicon expert meeting in Norderstedt, Germany in 2007, an Ethicon employee presented a PowerPoint entitled “Factors Related to Mesh Shrinkage” in which all of these issues were clearly laid out.⁹⁵ More recent studies have clearly demonstrated that mesh contraction/shrinkage increases the longer a mesh is implanted.⁹⁶

It is my opinion to a reasonable degree of medical certainty that as a result of work with internal and external experts and consultants in the late 1990s, multiple internal documents and articles, and the scientific literature as a whole, that GYNEMESH PS used in PROSIMA not only could, but would shrink and contract, and that this shrinkage could lead to painful complications in women implanted with PROSIMA, such as multiple erosions that can occur throughout one’s lifetime, chronic and debilitating pelvic pain, recurrence, worsening POP, de novo incontinence, chronic dyspareunia, nerve injury, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to vaginal walls, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others.

As a result, the polypropylene in Ethicon’s PROSIMA mesh is not suitable for its intended application as a permanent prosthetic implant for pelvic floor repair in women, and Ethicon failed to warn physicians and patients of the possibility of shrinkage and contraction and the adverse outcomes that could occur as a result.

⁹⁴ ETH.MESH03917375.

⁹⁵ ETH.MESH. 02017152 (Nordestadt Expert’s meeting 2007); ETH.MESH.01782867 (Factors Related to Mesh Shrinking).

⁹⁶ Mamy L, et al.: *Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection*. Int Urogynecol J. 2011 Jan;22(1):47-52 (using three-dimensional translabial ultrasonography found mean contraction of 30%, 65%, 85% at follow-up durations of 3, 6, and 8 years, respectively).

demonstrates that the pathological process that causes mesh shrinkage is progressive and there is a linear evolution of the contraction rate with time, raising the frightening possibility that mesh contraction syndrome continues indefinitely into the future.

6. The Mesh Used in the PROSIMA Deforms

The mesh used in the PROSIMA device deforms with tension upon insertion and subsequent to implantation due to various structural, inflammatory, foreign body responses, chemical processes and simply time causing the mesh to bunch, shrink, contract, curl, rope, fray, zip, have particle loss, and sharp edges. This deformation can lead to scar plate formation, fibrotic bridging, increased infections, erosions, permanent and debilitating pain, dyspareunia, urinary and defecatory dysfunction, damage to the vaginal walls, and nerve damage.

At the time of the launch of the PROSIMA, Ethicon had available and considered using absorbable and lighter weight meshes in the device. However, documents reflect that Ethicon chose not to do so in order to meet its launch deadline.

From my personal experience, deformed mesh is very difficult to remove often requiring multiple surgeries and, even once removed, many of the adverse conditions remain or are exacerbated. Ethicon had alternatives to including the heavyweight small pore GYNEMESH PS in the PROSIMA. These options may have mitigated some of the deformation and resultant adverse events associated with the GYNEMESH PS.

7. The Resin Used to Manufacture the GYNEMESH for PROSIMA Should Never Have Been Used as a Permanent Implant in the Vagina

According to Ethicon Medical Director, Dr. Martin Weisberg, a Material Safety Data Sheet (MSDS) is “a document that discusses the product, the composition, any potential hazards from it...”⁹⁷ As it relates to polypropylene, I have reviewed several MSDSs for polypropylene resin used to manufacturer meshes used in various pelvic floor meshes. All of the MSDSs discussed below are available to the public.

Sunoco, the manufacturer for the polypropylene resin used to manufacture Ethicon’s

⁹⁷ Weisberg Dep. (8/9/13) 909:2-9.

pelvic floor products lists the possibility that polypropylene mesh is incompatible with strong oxidizers. This is documented by the Sunoco MSDS⁹⁸ from April 13, 2005 which states in relevant part:

10. STABILITY AND REACTIVITY

• **INCOMPATIBILITY**

The following materials are incompatible with this product: Strong oxidizers such as chlorine, peroxides, chromates, nitric acid, perchlorates, concentrated oxygen, sodium hypochlorite, calcium hypochlorite and permanganates. Chlorine; Nitric acid;

This warning is important because it states that the polypropylene in the GYNEMESH PS is incompatible with strong oxidizers like peroxides, which is particularly important because the vagina is a natural and ready source of peroxides.⁹⁹ The human body also contains other agents, such as hydrocarbons and various bacteria that impact the polypropylene as discussed above.¹⁰⁰

The Prolene MSDS indicates that if you put the polypropylene used to make the GYNEMESH PS mesh in an environment with peroxides, it will start to break down. Given the information available to Ethicon concerning the dangers of polypropylene coupled with the warnings and other contents of the MSDSs and related documents, at a minimum, Ethicon should have conducted clinically relevant testing to determine if naturally occurring conditions in the vagina could cause polypropylene used in the PROSIMA to alter inside a woman's pelvis (as well as other complications). If so, what materials are released into the body as a result, and what

⁹⁸ ETH.MESH.02026591 at 6591-6595.

⁹⁹ Strus, M., "The in vitro effects of hydrogen peroxide on vaginal microbial communities," FEMS Immunol Med Microbiol, 2006 October; 48(1):56-63; Strus, M., "Hydrogen peroxide produced by Lactobacillus species as a regulatory molecule for vaginal micro-flora," Med Dosw Microbiol. 2004:56(1):67-77.

¹⁰⁰ HB Moon, "Occurrence and accumulation patterns of polycyclic aromatic hydrocarbons and synthetic musk compounds in adipose tissues of Korean females" 2011; "Determination of volatile purgeable halogenated hydrocarbon in human adipose tissue and blood stream," from Bulletin of Environmental Contamination and Toxicology Volume 23 Issue 1 pp 244 – 249 published in 1979; Environmental Health Perspective's, Vol. 60 pp. 127-131, Henry Anderson, "Utilization of Adipose Tissue Biopsy and Characterizing Human Halogenated Hydrocarbon Exposure," N. Das, Journal Biotechnology Research International 2010, Vol 2011, Article ID 941810 titled, "Review Article: Microbial Degradation of Petroleum Hydrocarbons Contaminant: An Overview", "Health, Safety and Environment Fact Sheet: Hazardous Substances from CAW/TCA." (www.caw.ca) August 2011, D. Lithner, 2011, entitled "Environmental and Health Hazards of Chemicals in Plastic Polymers and Products," University of Gothenburg.

impact would those materials have on the body. The fact that the mesh in the PROSIMA is susceptible to breaking down when in contact with peroxides makes it an unsuitable material to be placed in the vagina for the reasons discussed above. At the very least, Ethicon should have disclosed this information to physicians and patients considering use of their pelvic mesh.

The fact that the MSDS for the PROSIMA mesh warned against contact with strong oxidizers such as peroxides is information that a doctor would want to consider before implanting a permanent device in a woman's body for the rest of her life as substances in the vagina could cause the breakdown of the product, yet Ethicon never informed doctors about the warning in the MSDS. As a result, Ethicon failed to provide physicians with adequate information upon which to make a treating decision about whether to use PROSIMA or how to treat complications from the device, and in turn prevented patients from receiving such information.

In addition to these undisclosed risks of degradation set forth in the MSDS due to mesh placement in the vaginal space, Ethicon also failed to inform patients and physicians that the polypropylene it used was potentially carcinogenic.

Sunoco, the manufacturer for the polypropylene resin used to manufacture Ethicon's pelvic floor products specifically notes the possibility that polypropylene mesh can cause tumors or cancer. The Sunoco MSDS¹⁰¹ from April 13, 2005, states in relevant part as follows:

15. OTHER INFORMATION

Follow all MSDS/label precautions even after container is emptied because it may retain product residue.

COMPONENT TOXICITY: Polypropylene has been tested in laboratory rats by subcutaneous implantation of discs or powder. Local sarcomas were induced at the implantation site.¹⁰²

¹⁰¹ ETH.MESH.02026591 at 6591-6595.

¹⁰² *Id.* at 02026595.

Dr. Martin Weisberg, Ethicon Medical Director, is not only familiar with this MSDS, he also has personal experience with it. Dr. Weisberg testified that the manufacturer of Ethicon's mesh did a study by implanting it under the skin of rats and it did in fact induce sarcomas.¹⁰³ Dr. Weisberg also agrees "if there was evidence of cancer-causing abilities of polypropylene . . . a reasonable doctor would want to know."¹⁰⁴ Dr. Weisberg is not aware of any instance when Ethicon "disclosed to any doctor that there's any evidence that the use of polypropylene mesh might induce sarcomas in its patients."¹⁰⁵

Dr. David Robinson, a former Ethicon Medical Director, testified he was unaware of Ethicon ever performing any studies or research to determine whether polypropylene could cause cancer in the long term.¹⁰⁶ In addition, he testified that Ethicon never disclosed "the potential that polypropylene in the product could be cancer causing."¹⁰⁷ Dr. Robinson also testified that it would be reasonable for physicians to want to know about polypropylene possibly causing cancer.¹⁰⁸

I have also reviewed several MSDSs for polypropylene resin used in manufacturing various other pelvic floor meshes. Generally, these MSDSs also contain information about potential degradation from oxidation and the risks of carcinogenicity and expressly state that polypropylene products should not be used for permanent implantation in the human body. All of the MSDSs discussed below were and are available to the public, including Ethicon. An MSDS from Chevron Phillips,¹⁰⁹ a manufacturer of polypropylene resin states:

MEDICAL APPLICATION CAUTION: Do not use this Chevron Phillips Chemical Company LP material in medical applications involving permanent

¹⁰³ Weisberg Dep. (8/9/13) 951:6-10.

¹⁰⁴ *Id.*

¹⁰⁵ *Id.* at 951:11-16.

¹⁰⁶ Robinson Dep. (9/11/13) 1105:17-110:14.

¹⁰⁷ Robinson Dep. (9/11/13) 1114:15-18.

¹⁰⁸ Robinson Dep. (9/11/13), 1115:5-19.

¹⁰⁹ Chevron Materials Safety Data Sheet Marlex Polypropylenes (All Grades) Revision Number: 3 (Ex. T-3137).

implantation in the human body or permanent contact with internal body fluids or tissues.

Do not use this Chevron Phillips Chemical Company LP material in medical applications involving brief or temporary implantation in the human body or contact with internal body fluids or tissues unless the material has been provided directly from Chevron Phillips Chemical Company LP under an agreement which expressly acknowledges the contemplated use.

Chevron Phillips Chemical Company LP makes no representation, promise, express warranty or implied warranty concerning the suitability of this material for use in implantation in the human body or in contact with the internal body fluids or tissues.

With respect to the Chevron Phillips MSDS, Ethicon Medical Director, Dr. Martin Weisberg, testified that he did not have the Chevron Phillips MSDS in 2001 when he reviewed the Sunoco MSDS and no one at Ethicon alerted him to it.¹¹⁰ If he had been alerted to the Chevron Phillips MSDS, it may have “triggered” an investigation on his part.¹¹¹ He also believes that if Ethicon knew about this MSDS, Ethicon should have studied the issue and, if they did not do so, it would have been a violation of the company Credo.¹¹²

Total Petrochemicals, the polypropylene resin manufacturer for the polypropylene used in AMS’s pelvic floor products, Technical Data Sheet for Polypropylene PPR 7220, states in bold red lettering “Under no circumstances are any products sold by Total Petrochemicals suitable for human or animal implants.” It further states that, “The above-mentioned product is NOT in compliance with the US pharmacopoeia because we DID NOT perform required tests.”¹¹³

The fact that this information has not been disclosed to physicians in any manner (IFUs, direct letters or promotional materials) is especially concerning in light of literature showing reports of cancer associated with polypropylene. Specifically, there have been cases of

¹¹⁰ Weisberg Dep. (8/9/13) 944:16-945:5.

¹¹¹ *Id.*

¹¹² *Id.* at 947:4-19.

¹¹³ ETH.MESH.02026591 (emphasis in original).

pseudotumor reported in polypropylene for hernia mesh¹¹⁴ and inflammatory myofibroblastic tumor of low malignant potential with a TVT device.¹¹⁵ In addition, there have been 2 cases of bowel cancer associated with mesh used for abdominal sacrocolpopexy, one associated with mersilene and one with polypropylene and TVT placement.¹¹⁶ A case of primary vaginal leiomyosarcoma associated with TVT and anterior repair with Bard Duraderm has also been reported.¹¹⁷ Finally, a report of angiosarcoma associated with Darcon vascular grafts was reported in 1999.¹¹⁸ The authors of this article noted at least 8 other sarcomas developing at the site of vascular prosthesis, and that the rate of these sarcomas, associated with foreign bodies, was much higher than the rate of sarcomas in general. All sarcomas associated with Dacron grafts were high grade histology and disseminated at the time of presentation. They also note that the latency period from the acquisition of the foreign body and the development of sarcoma had a mean of 33 years. They document that a chronic foreign body reaction, the same “microscopic foreign body reaction” described by Dr. David Robinson in his Sept 2013 deposition as being clinically insignificant, was the etiology of this carcinogenesis. The authors also describe sarcomas developing in rodents after inert plastic polymers were placed in their soft tissue: “The sarcomas developed in rodents in which thick fibrous capsules developed around the implanted material.” The authors conclude: “For unknown reasons, the cells in this inflammatory and repair process may undergo a malignant transformation, probably associated with oncogene activation and tumor suppressor gene inactivation. Further studies are warranted to search for the mechanisms involved in foreign body tumorigenesis.” To my knowledge, to date no manufacturer of mesh products has investigated this oncogenic potential as the authors

¹¹⁴ Karrem, M., Community Oncology, Volume 7/Number 4/April 2010.

¹¹⁵ Kwon S., et al, Female Pelvic Med Reconstruct Surg, Volume 18, Number 4, July/August 2012.

¹¹⁶ Ahuja, S., et al, Gynecol Surg 2011, 8:217-221.

¹¹⁷ Moller, K., et al, Gynecologic Oncology 94 (2004) 840-842.

¹¹⁸ Ben-Izhak, O., et al, Am J Surg Pathology, Issue: Volume 23 (11), 1999, p. 1418.

recommended.

In a report from the International Agency for Research on Cancer: *Surgical Implants and Other Foreign Bodies*, “When several polymers were tested in rats according to the same experimental protocol, sarcoma incidences ranged from 70% (polypropylene) to 7% (silicone).”¹¹⁹ “Polymeric implants prepared as thin smooth films (with the exception of poly(glycolic acid)) are POSSIBLY CARCINOGENIC TO HUMANS.”¹²⁰ Given the fact that hernia mesh placement increased in the 1990's with the advent of laparoscopic placement, and that vaginal mesh placed for SUI and POP accelerated in the 2000's, we may be on the cusp of an ever increasing number of foreign body tumors associated with vaginal mesh.

Ethicon did not undertake any long term testing to determine whether or not these warnings on the polypropylene resin manufacturers MSDS were associated with long term consequences for permanent human use. This is true despite the fact that Ethicon has knowledge of three of these cancer reports (Kwon, Moller and Ahuja) as they are referenced in Ethicon's 2013 Clinical Evaluation Report regarding the Prolene mesh used in Ethicon's stress urinary incontinence product, the TVT.¹²¹

Additionally, there is no evidence that Ethicon made any effort to inform surgeons of important information contained in various Manufacturer Safety Data Sheets (MSDS) regarding the use of polypropylene. This information includes the dangers of using polypropylene in a permanent implanted medical device and that laboratory studies on rats showed that polypropylene caused sarcomas in laboratory rats. Clearly, these facts are critical information relevant to both the surgeon evaluating his or her treatment options and to the patient's informed consent decisions. For example, a physician who is informed of these issues can better assess his

¹¹⁹ *International Agency for Research on Cancer, Summaries and Evaluations*, Vol.:74 (1999).

¹²⁰ McGregor, D.B., et al, *European Journal of Cancer* 36 (2000) 307-313 (emphasis added).

¹²¹ ETH.MESH.10150515.

patient for the risk of these cancers – without this knowledge from Ethicon, he or she may have no reason to suspect a cancer risk or the need for cancer treatment.

B. The PROSIMA Was an Ill-Defined Procedure Without Any Clinical Evidence that It Was Effective or Safe

As shown above, the clinical data for PROSIMA prior to launch was very limited. The early Carey studies used prototype devices that differed significantly from the PROSIMA (for example, different mesh shapes, different surgical paths and no balloon). Moreover, the studies were generally uncontrolled and largely limited to the inventor of the device who had a financial interest in the outcome of the studies (in fact, being paid for publication of the results). In my opinion, these studies provide little to no evidence of the efficacy or safety of the device ultimately marketed as the PROSIMA device other than the adverse events associated with mesh implantation.

The Ethicon-sponsored multi-center study provides a higher level of evidence regarding the effectiveness and safety of the PROSIMA device. On efficacy, this study failed in its pre-defined primary endpoint – that is, it failed to demonstrate that the PROSIMA was successful in treating pelvic organ prolapse as defined by the investigators prior to study initiation. The study did show some evidence of improvement in its secondary endpoints. It was evident in this study that the results varied greatly across the various centers, so much so that, upon receipt of the six-month data Ethicon delayed the launch of PROSIMA. This factor is critical because Ethicon intended the PROSIMA for use by “generalists” or physicians who were less well-trained in pelvic floor repair.¹²² It was to be a “standardized technique” and “less technically

¹²² ETH.MESH.00190766 (June 2005 Project Mint Charter Presentation) (“Develop a procedural kit for the surgeon performing pelvic floor repairs entailing a less technically challenging, standardized technique which will improve functional outcomes over traditional native tissue and current flat mesh repairs and will be applicable for most cases of pelvic organ prolapse.”); ETH.MESH.03573604.

challenging.”¹²³ However, as demonstrated by the variability of the results in the clinical trials, it is evident that the technique was not standardized and outcomes varied widely (from 16% in one center to 90+% in another – the site run by the inventor who had a financial interest in the outcomes). Regarding the vaginal support device, the lead investigator commented that: “There did appear to be a learning curve with VSD fitting, with some of the early losses associated with selection of a larger than necessary VSD and not placed sufficiently high within the vagina.”¹²⁴ The study also showed an 8% erosion rate at one year, 9% at two years, with one erosion appearing at 28 months. In my opinion, this study does not demonstrate that the PROSIMA is a safe and effective device or method for treatment of pelvic organ prolapse. An internal Ethicon document noted that, even after this study, there was an “evidence gap” regarding the safety and efficacy of PROSIMA.¹²⁵

The Carey head-to-head trial also failed to demonstrate that the PROSIMA was superior to traditional native tissue repairs. Moreover, the patients in the study experienced more frequent and severe adverse outcomes related to the implantation of the mesh. In my opinion, this study demonstrated that PROSIMA was, at best, as effective as traditional repairs with an increase in severe, debilitating adverse events and complications. Year’s earlier members of Ethicon’s PROSIMA team recognized that it would not be responsible to market the PROSIMA if it was not shown to be superior to traditional surgeries because of the increased risks associated with mesh. In September 2005, Martin Weisberg, Ethicon Medical Director, noted that it would make no sense to market a device that was no more efficacious than native tissue repair especially if such a device carried increased risks of permanent mesh implantation. He wrote:

¹²³ *Id.*

¹²⁴ ETH.MESH.01193011 at 032.

¹²⁵ HMESH_ETH_02687589 at 22.

From what I understand this study proposes to demonstrate "the non inferiority of anterior MINT, posterior MINT and combined anterior/posterior MINT versus anterior colporrhaphy, posterior colporrhaphy and a combined anterior/posterior colporrhaphy." Have we discussed this with marketing? Why would we want to introduce a synthetic graft product that does no better than a native tissue repair???

Why would anyone spend any money on a device, and take what they consider a risk of using a graft when they could get the same results for free with native tissue? If we are not confident that this will be better than what our marketing has been claiming is inadequate (native repair) why bother pursuing? If we are confident that we will be able to claim superiority, then we should go for it.¹²⁷

His sentiments were echoed by the marketing team as well. In a September 6, 2005, e-mail Allison London Brown wrote: "[I] would in general agree with Marty's comment on superiority. We need to show that we are providing some type of benefit on the new products we launch, otherwise what is the value to the customer."¹²⁸ The Carey study failed to show superiority and did, indeed, show mesh-related adverse events such as erosions. The device should not have been marketed under any standards, including Ethicon's own. In the original Charter document for the PROSIMA project, Ethicon's Risk Assessment – Clinical noted a potential risk: "The clinical results seen from the Carey/Slack evaluation are not favorable."¹²⁹ The mitigation strategy for this risk: "Change scope of project or abandon." At this point, Ethicon had numerous clinical results that were not favorable – it should have followed its own mitigation strategy and abandoned the PROSIMA project.

Numerous Ethicon Key Opinion Leaders and other physicians interviewed by Ethicon voiced their concern about the PROSIMA and particularly the idea that it should be used by inexperienced or undertrained physicians. In April 2008, Ethicon was informed that one of its most prominent Key Opinion Leaders, Vincent Lucente, "was quite scathing of PROSIMA™

¹²⁶ ETH.MESH.03048665

¹²⁷ ETH.MESH.03048664

¹²⁸ ETH.MESH.03048783

¹²⁹ ETH.MESH.03573604 at 33.

being a reckless product.”¹³⁰ At an Incontinence Summit in 2009, Ethicon presented the clinical data from its sponsored study to key opinion leaders. Feedback from the physicians at the Summit conference was uniformly against the safety and efficacy of PROSIMA.¹³¹ Several KOLs “voiced concerns that it could be surgical success rate of stitch repairs with a mesh complication rate higher than Prolift.”¹³² Another Ethicon employee reported:

The feelings were very negative towards PROSIMA, and the main points of contention are summarized below. First, the target audience appears to be less skilled generalists. Why would we want to put a product with questionable data in this groups hands. [T]he potential patient complications for mesh with PFR is too great to put something like this in the hands of generalists. The quotes I've heard over and over from numerous KOLs were, big mistake, don't do it.... One KOL said they would no longer work with the company as a matter of principle if we launched PROSIMA.¹³³

Piet Hinoul wrote that the proper use of the mesh requires significant skill. “[I]t is also clear to me that this PROSIMA is not the mesh for dummies, as I had thought when I first saw its description.” Dr. Hinoul also discussed that the device would only be appropriate, if for anyone, for Grade II repair.¹³⁴

C. The PROSIMA IFU Did Not Contain or Understated the Known Risks of the PROSIMA Device

The purpose of the IFU is for a medical device manufacturer to provide physicians with

¹³⁰ ETH.MESH.05009194

¹³¹ ETH.MESH.00281482 (“I’ve reviewed my notes in the meeting and a transcript and the synopsis is attached. As you review them, you will find a fairly recurring theme that objections to PROSIMA™ came up in virtually every venue regardless of what topic was being discussed.” The notes also stated: “A second recurring theme was that it did not make sense to use mesh in people with lesser degrees of prolapse given the outcomes.”).

¹³² ETH.MESH.00281482

¹³³ ETH.MESH.00548923

¹³⁴ As noted above, the initial objectives for Prosima included broad use across all grades of POP and Ethicon submitted the 510(k) and received clearance for this broad use. Recognizing the limitations of the device for grades I and IV, Ethicon targeted its marketing at grade II and III prolapse. This presented a concern for regulatory. *See, e.g.,* Regulatory Strategy for the Promotion of GYNECARE PROSIMA Pelvic Floor Repair Systems for Specific Use - RAXXXX-2009 (December 6, 2009). “GYNECARE PROSIMA has a general indication, but has been promoted for specific use with symptomatic moderate prolapse, Stage II and III.” ETH.MESH.00077702. Per Dr. Hinoul’s concerns, Ethicon, at a minimum, should have further limited the scope of its marketing to only grade II prolapse.

the information necessary for them to make decisions regarding the use of a medical device for a particular patient. In addition, the IFU should disclose adverse reactions and risks known to the medical device manufacturer to the physician so that the risks can be relayed to the patient and an informed decision regarding the use of the product can be reached. Also, an IFU must provide information that would allow a physician to properly assess, diagnose and safely treat a woman who has presented with a complication related to that device.

Throughout my education, training, surgical and clinical practice, I have reviewed numerous IFUs for a variety of products, including mesh products in order to understand the proper way to use the device and to gain knowledge about the complications and adverse events associated with a device. I have extensive clinical experience with IFUs and instructing patients about the adverse events/risks contained in the IFU. Similar to Medical Directors, Dr. Martin Weisberg and Dr. David Robinson, I have gained expertise in IFUs through my extensive clinical experience reviewing IFUs, and consenting patients regarding IFUs, including Ethicon's own pelvic mesh products including the TVT line and Prolift.

Catherine Beath, Ethicon's former Vice President of Quality Assurance and Regulatory Affairs, testified that "physicians should be made aware of all the significant safety risks associated with the product in the IFU."¹³⁵ And, "a reasonably prudent medical device company would continually update the label consistent with developing data and information that becomes known to the company" when it is appropriate.¹³⁶ Similarly, former Medical Director Dr. David Robinson testified that the warnings and adverse event section of the IFU should include all significant risks and complications related to the procedure and the mesh.¹³⁷

According to Dr. Robinson, a device manufacturer must include this information because

¹³⁵ Beath Dep. (7/12/13) 592:7-11.

¹³⁶ Beath Dep. (7/11/13) 198: 8-13.

¹³⁷ Robinson Dep. (9/11/13) 238:12-25.

you want to make sure the doctors have all the information they need to adequately inform patients who are deciding to use the product.¹³⁸ Dr. Weisberg agrees that an IFU should not knowingly underestimate the risks of using the product.¹³⁹ And, if an IFU excludes known complications or understates the risks, it “fails in one of its principal purposes.”¹⁴⁰ Finally, Peter Cecchini, a 43 year Ethicon employee and Regulatory Fellow, testified that the “regulatory standard for the IFU is the known risks are supposed to be included in the adverse reactions.”¹⁴¹ Mr. Cecchini testified that he relies on medical affairs to make sure he knows the known risks so they can be included in the IFU.¹⁴² Based on my professional experience, review of the scientific literature, the PROSIMA IFU and other IFUs, and internal Ethicon documents, it is my opinion that Ethicon’s IFU failed to include “the known risks” of the PROSIMA device/procedure and “underestimated” the frequency and severity of the risks it did include. Hence, Ethicon’s IFU did not properly inform treating physicians about the lack of evidence supporting the efficacy of the PROSIMA or the frequency and potentially life-altering risks of the device. In addition, the risks included were underestimated as to frequency and severity and misleading as to the cause. Finally, the IFU failed to inform physicians regarding safe and effective management of women who presented with mesh-related complications.

1. Ethicon Failed to Disclose Known Risks in its IFU

As noted above, there are many significant and risks associated with the PROSIMA mesh and the procedure to implant that mesh. Many of these risks were not disclosed in the PROSIMA IFU. Importantly, when PROSIMA was launched in late 2009, Ethicon had included many of these risks in the IFUs for its other pelvic floor products, including PROLIFT. In

¹³⁸ Robinson Dep. (9/11/13) 239:1-11.

¹³⁹ *Id.* at 960:13-16.

¹⁴⁰ *Id.* at 961:10-17.

¹⁴¹ Cecchini, 10/22/12, 65:5-12.

¹⁴² Cecchini, 10/22/12, 65:18-24.

addition, in Ethicon's current GYNEMESH PS (the mesh used in the PROSIMA) IFU, many of these risks now appear. Ethicon's lead scientists and medical personnel have testified that Ethicon was aware of these risks long before the PROSIMA was marketed. The PROSIMA IFU did not include the following all of which would be important information for a treating physician:

1. As shown in the above clinical trials, the PROSIMA device and procedure were never standardized leading to large variability in outcomes;
2. As shown in the clinical trials, the safety and effectiveness of this device has not been adequately established and the studies that were done often used materially different devices and techniques;
3. Treatment for complications from PROSIMA may require one or more surgical procedures which may only temporarily or incompletely resolve those complications, may exacerbate them or cause new serious additional complications, and the mesh may never be able to be completely removed (compare GYNEMESH PS IFU "One or more revisions surgeries may be necessary to treat these complications.... In cases where the GYNECARE GYNEMESH needs to be removed in part or whole, significant dissection may be required");¹⁴³
4. Prosima can cause permanent groin and/or leg pain, buttocks pain, weakness, numbness and nerve irritation (compare GYNEMESH PS IFU: "Neuromuscular problems, including acute and/or chronic pain in the groin, thigh, leg, pelvic and/or abdominal area may occur");
5. The PROSIMA mesh can erode into the vagina, or other organs and can be severe and recur repeatedly for the rest of the woman's life;
6. The IFU falsely states that complications are "unlikely" or "self-resolving" when the PROSIMA may cause permanent and severe urinary and voiding dysfunction, sexual dysfunction, permanent and severe chronic pain, permanent and severe pain with intercourse and total loss of sexual desire or enjoyment (compare GYNEMESH PS IFU: "pelvic pain or pain with intercourse, which in some patients may not resolve");
7. PROSIMA mesh causes a foreign body response that can be chronic causing inflammation (that is not "slight" or "transient"), severe pain and infections.
8. PROSIMA mesh can cause fibrotic bridging, formation of a scar plate and permanent scarring in the vagina;
9. PROSIMA mesh may cause injury to a patient's partner during intercourse (compare GYNEMESH IFU: "Exposed mesh may cause pain or discomfort to the patient's partner during intercourse");
10. Complications from PROSIMA can occur years after implantation and can

¹⁴³ By referring to these IFUs, I do not mean to imply that the current GYNEMESH PS IFU or the last PROLIFT IFU are or were adequate, but only to demonstrate that Ethicon had full knowledge of these risks and failed to address them at all or truthfully in the PROSIMA IFU.

- reoccur or be permanent;
11. Risk of death (compare GYNEMESH PS IFU “Death”);
 12. PROSIMA should be used with caution in women with immune system disorders (compare GYNEMESH PS IFU: “In patients with compromised immune systems or other conditions that could compromise healing, the risks and benefits should be weighed carefully.”);
 13. PROSIMA may cause de novo incontinence (compare GYNEMESH IFU: “Prolapse repair may unmask pre-existing incontinence conditions.”);
 14. PROSIMA can cause wound dehiscence, urge incontinence, urinary frequency, urinary retention or obstruction, recurrent prolapse, erosion into other structures or organs (compare GYNEMESH PS IFU);
 15. Patients with prior pain syndromes are at a heightened risk of mesh failure and resulting complications including new onset of pain, aggravation of pain, and resulting permanent irreversible pain that may continue to get worse over time with or without the presence of the mesh.¹⁴⁴

2. Clinical and Safety Information to be Included in IFU For Prolift Not Implemented for Prosima

In 2007, Ethicon had agreed that it would be more appropriate to place Warnings and Adverse Reactions at the beginning of an IFU (before the description of the surgical procedure).¹⁴⁵ Although Ethicon made these changes to its PROLIFT IFU, it did not do so for PROSIMA. In addition, Ethicon added clinical trial information into the PROLIFT IFU – again, it did not do so for the PROSIMA. In my opinion, these changes were necessary and critical to properly communicate the efficacy and safety profile of PROSIMA. A physician reviewing these adverse reactions and seeing that the data on efficacy was very poor might very well choose not to use the device. By refusing to make these changes (as it had done for PROLIFT) Ethicon removed the physician’s ability to make an informed decision and to have an informed conversation with his or her patients. For example, prior to the marketing of the device in December 2009, Ethicon had available, at a minimum: (1) the Carey investigational data (and the fact that the data showed 30%+ failure rate when properly accounting for loss to follow-up); (2) the Carey head to head data showing PROSIMA was not superior to traditional techniques but

¹⁴⁴ ETH.MESH.00070065

¹⁴⁵ ETH.MESH.00372330.

exhibited a higher complication rate, including erosions; and, (3) its own sponsored study data which failed to meet its pre-specified endpoint for success. This information should have been included in the PROSIMA IFU.

In addition, Ethicon possessed data demonstrating that certain patient populations were more likely to experience adverse outcomes from the PROLIFT. As there is no reason to believe PROSIMA would have materially different classes of outcomes for those patient populations, the information should have been included in the PROSIMA IFU.¹⁴⁶ Dr. Hinoul, Ethicon's Medical Affairs designee, testified at the FDA Obstetrics and Gynecology Devices Advisory Committee meeting in September 2011 that certain patient populations were at higher risk for complications from the PROLIFT System and testified in his deposition that Ethicon was aware of this fact since the time of the PROLIFT launch.¹⁴⁷

3. Information and/or Training to Deal Safely and Effectively with Complications from Mesh

Ethicon's PROSIMA IFU should have contained information about training and management of complications resulting from POP procedures. Moreover, Ethicon never provided any information about how to properly deal with mesh complications. This is of particular concern here because as noted above Ethicon targeted less-experienced physicians as the primary market for the PROSIMA. As early as 2005, Ethicon had VOC feedback that "[a]mong generalists, an intensive education program is required to address basic science of mesh, surgical up-skilling and mgmt. of complications."¹⁴⁸ Having this information in the IFU

¹⁴⁶ Catherine Beath deposition, 3/26/12, 114:2-115:12

¹⁴⁷ Piet Hinoul deposition 4/6/12, 480:8-480:20; Hinoul FDA Advisory Committee Testimony at pg 145 ("One of the most important questions we need to ask ourselves is also why these adverse events are occurring. And the risk factors for mesh exposures are becoming more and more apparent. Several studies published this year show that hysterectomy, patient age, smoking, diabetes, and surgeon experience predispose patients to mesh exposure. Patient selection and risk factors, appropriately stated in the device's labeling, as well as the surgeon's training, are therefore part of our proposal.")

¹⁴⁸ ETH.MESH.00190766 at 790.

would also ensure physicians were getting scientifically sound, evidenced back information and training on how to treat complications.¹⁴⁹

4. Degradation and Carcinogenicity

As discussed above, the mesh used in the PROSIMA has been shown to degrade in the vaginal environment and to be carcinogenic. Moreover, the manufacturers of the resin used to create the polypropylene mesh in PROSIMA warned that it was not compatible with an environment such as the vagina. Ethicon should have included these warnings in its IFU to allow physicians and patients to make fully informed decisions about the risks of using PROSIMA.

V. CONCLUSION

Based on my experience and training, my review of the relevant scientific literature and my review of relevant documents internal and external to Ethicon, it is my opinion within a reasonable degree of medical and scientific certainty that: (1) the mesh used in the PROSIMA device is not suitable for permanent implantation in the human body; (2) there is insufficient sound clinical evidence supporting the safety or efficacy of the PROSIMA device or procedure; and (3) Ethicon failed to provide physicians and patients with accurate, complete information about the risks and lack of efficacy with the PROSIMA device and procedure.

¹⁴⁹ In lieu of appropriate scientific information being provided in the IFU, Ethicon's sales representatives (not medical personnel) provided physicians with non-evidenced based methods to treat complications typically called "tips & tricks." For example, in one e-mail exchange regarding two erosions with the sales representatives shared their experiences with how to treat an erosion.

I have a docs who just had two Prosima patients come back ... one with a midline posterior exposure and a second with an anterior apex exposure. Neither patient had a concomitant hysterectomy with the procedure. My doc was wondering if there were any specific tips on how to reduce the exposure rate. We discussed getting into the right space, hydrodissection ... he thought he was doing both of those. Just curious if either of you had any tips. ETH.MESH.13305875 at 876.

Signed this 1st day of February 2016.

X 
Bruce Rosenzweig M.D.